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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61M 1/16, A61K 33/14

A1

(11) International Publication Number: **WO 00/44418**

(43) International Publication Date: 3 August 2000 (03.08.00)

(21) International Application Number: PCT/EP00/00130

(22) International Filing Date: 7 January 2000 (07.01.00)

(30) Priority Data:
MI99A000176 29 January 1999 (29.01.99) IT

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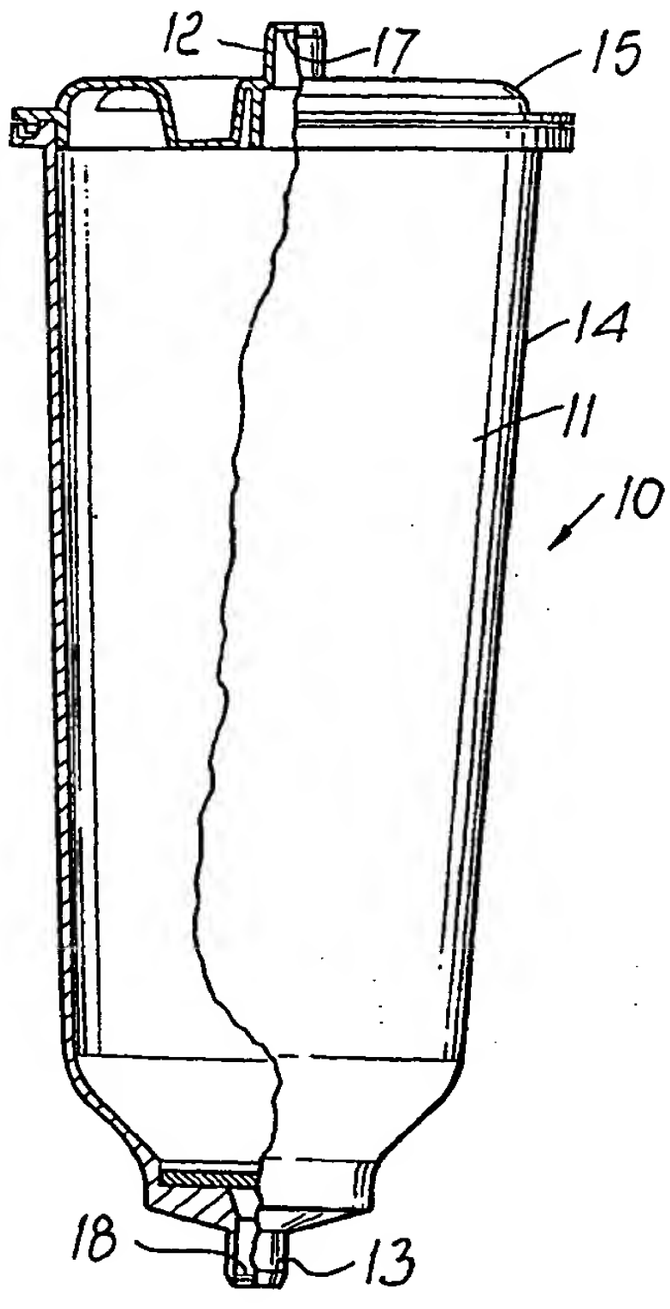
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: CARTRIDGE FOR DIALYSIS CONTAINING SODIUM BICARBONATE

(57) Abstract

A cartridge (10) is provided containing sodium bicarbonate in solid form. The cartridge (10) is usable in a haemodialysis machine for continuously producing a buffer solution, which is mixed with another solution to produce a dialysis solution. The cartridge (10) also contains a solid acid or acid anhydride, or carbon dioxide gas. This has been found to overcome problems caused by a temporary high pH in the dialysis solution during the early stages of a dialysis operation.



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CARTRIDGE FOR DIALYSIS CONTAINING SODIUM BICARBONATE

This invention relates to dialysis cartridges containing solid sodium bicarbonate.

BACKGROUND

It has long been known to use cartridges containing drugs, or other substances, in solid form and to pass water or a solution through the cartridge to dissolve the solid substance continuously, e.g. for continuous administration to a patient.

Examples are WO-A-86/03417 and US-A-4432756.

It is also known, as disclosed in EP-A-0278100 to provide sodium bicarbonate in solid form for use as a buffer in haemodialysis. Sodium bicarbonate is stored separately from the rest of a dialysis solution, which contains calcium and magnesium ions, to prevent calcium and magnesium carbonate precipitation. A cartridge of sodium bicarbonate powder is inserted in a haemodialysis machine and water is passed through the cartridge. The powder is gradually dissolved, so that a solution of sodium bicarbonate is continuously produced. The solution is continuously flowed through the machine, mixing with the rest of the dialysis solution in-line upstream of the dialyzer. There is, therefore, only a short dwell time in the machine after mixing, so that the problem of calcium and magnesium carbonates being precipitated is avoided.

A problem does, however, arise with such cartridges. The pH of the mixed dialysis solution is monitored upstream of the dialyzer. If the pH falls outside a given range, then an alarm is triggered. It has been found that this often happens during the first twenty minutes of flow, when the machine is being set up for operation. After this period, no

problems are encountered. This causes substantial inconvenience to personnel operating haemodialysis machines, since the problem has to be investigated and the machine reset, each time the alarm is triggered.

The inventors have discovered that the problem is probably caused by contamination of the sodium bicarbonate powder with a small amount of sodium carbonate. The bicarbonate is less soluble than the carbonate, so that a high pH is caused by the dissolution of the carbonate in the early stages. Once the carbonate has dissolved, the problem disappears. It is, however, difficult and expensive to produce a sodium bicarbonate powder, which is not contaminated with sodium carbonate.

A possible solution to the problem once it was realised that sodium carbonate precipitation was the cause, would be to introduce a further line upstream of the pH monitoring device to add dilute acid solution to the dialysis solution during the first twenty minutes of use of the cartridge. This could be done upstream or downstream of the cartridge. This involves, however, modification of the dialysis solution, use of an additional solution and additional operational control.

The inventors have found that the problem can be relatively simply solved by modifying the contents of the cartridge.

SUMMARY OF THE INVENTION

The present invention relates to a cartridge having an openable sealed inlet and an openable sealed outlet, for connection in-line in a haemodialysis machine for passage of water, or a solution through the cartridge, the cartridge containing sodium bicarbonate in solid form.

In accordance with the invention, the cartridge additionally contains an acid, or acid anhydride in solid form, or carbon dioxide gas.

When the cartridge is mounted in a haemodialysis machine and water is passed through the cartridge, the acid or acid anhydride (including carbon dioxide) is gradually dissolved, decreasing the pH of the resulting solution to counteract any temporary increase in pH caused by sodium carbonate contamination.

The amount of acid or acid anhydride provided is preferably predetermined, so that it is leached from the cartridge during the initial 10 to 30 minutes, i.e. during the period that sodium carbonate is also likely to be leached from the cartridge.

Carbon dioxide may be added to the cartridge, during manufacture, in solid form, i.e. as dry ice, prior to sealing the cartridge.

Acids which may be used in solid form may be organic acids, e.g. citric acid, or tartaric acid, citric acid being preferred for clinical acceptability.

The cartridge may contain at least 0.2g of acid, or acid anhydride per 1000g of sodium bicarbonate; preferably at least 0.5g per 1000g and most preferably at least 1g per 1000g. The preferred embodiment contains 2.7g per 1000g.

DRAWINGS

The invention is described with reference to the accompanying drawings, wherein:-

Fig 1. is a side elevation of a cartridge according to the invention, shown partly in cross-section; and

Fig 2. is a diagrammatic illustration of the cartridge of fig 1 connected in a haemodialysis machine.

PREFERRED EMBODIMENTS

The currently preferred embodiments of the invention are now described. The construction of haemodialysis machines is well known, as is the construction of a sodium bicarbonate cartridge for use in a haemodialysis machine. The machine and the cartridge are not, therefore, described in detail. The cartridge may be of the type sold under the trademark EASYCART by Bieffe Medital S.p.A. of Italy.

The cartridge 10 comprises a body 14, closed by a lid 15 and defining a chamber 11. The body and lid are injection moulded in polypropylene. The chamber 11 contains sodium bicarbonate in granular, crystalline form, although other solid forms are possible. The lid 15 is sealed to the body 14 by ultrasonic welding. The lid 15 has an inlet 12 and the body had an outlet 13, both sealed closed in the as-moulded state, by integral membranes 17, 18 respectively.

The cartridge 10 is connected in-line in a first line 20 for receiving deionised water at 21 and supplying sodium bicarbonate solution to a main line 22, at 23. The membranes 17, 18 are perforated during clamping of the cartridge into the machine, by piercing means provided on the machine. The main line 22 also receives deionised water at 24. A container 30, containing a solution of the other ingredients of a dialysis solution, is connected to the main line 22 by a second line 25 at 26. A final dialysis solution is formed at point 26 and the main line 22 feeds this

to a dialyzer 40. A pH detector 50 is connected to the main line 22 downstream of point 26 and upstream of the dialyzer. The detector is connected with a control system (not shown), which produces an alarm, if a pH outside a predetermined range is exceeded. This range is usually 6.8 to 7.9 pH may be monitored by other means, such as by conductivity measurement.

The solution in the container 30 may contain any of the components usually provided in a dialysis solution, such as calcium and magnesium chloride, sodium chloride and an osmotic agent, such as dextrose.

In accordance with the present invention, the cartridge contains, in addition to the sodium bicarbonate, an acid or acid anhydride in solid form, or carbon dioxide gas, so as to avoid any sodium carbonate contamination causing a temporary increase in the pH of the dialysis solution to a degree sufficient to exceed the predetermined threshold and trigger an alarm.

The preferred embodiment of a cartridge contains 750g sodium bicarbonate and 2g citric acid, both in granular, crystalline form. A similar weight ratio could be used with different amounts of sodium bicarbonate.

Alternatives to citric acid are preferably provided in the same weight ratio.

Tests were carried out using cartridges containing 750g sodium bicarbonate and citric acid, tartaric acid, or carbon dioxide (added as dry

ice) respectively. These were compared with similar cartridges, to which no acid or carbon dioxide had been added.

The tests were carried out by running an Integra (trademark) haemodialysis machine, using the various cartridges. Notes were made of which cartridges produced an alarm signal, due to the pH of the mixed dialysis solution falling outside the predetermined range. The actual maximum pH of each solution was also recorded. "Acid" solutions, ie the solutions carrying the other components of the dialysis solution, were standard solutions produced by Gambro. In each case, the pH of the water supplied was 6.1. The results are shown in the tables below. There were numerous false alarms with the reference cartridges, but no false alarms with the cartridges according to the invention.

Table 1

This shows the results using the reference cartridges, containing 750g sodium bicarbonate and no added acid or carbon dioxide.

Sample No.	Maximum pH of dialysis solution	Alarm Yes/No
1	7.9	No
2	7.8	No
3	8	Yes
4	8.1	Yes
5	7.9	No
6	8	Yes
7	8.2	Yes
8	8	Yes
9	7.4	No
10	7.4	No

Table 2

This shows the results using cartridges according to the invention, containing 2g citric acid and 750g sodium bicarbonate.

Sample No.	Maximum pH of dialysis solution	Alarm Yes/No
11	7.5	No
12	7.5	No
13	7.5	No
14	7.5	No
15	7.4	No
16	7.4	No
17	7.4	No
18	7.4	No
19	7.4	No
20	7.4	No
21	7.4	No

Table 3

This shows the results using cartridges according to the invention, containing 0.5g or 1g of carbon dioxide (dry ice) and 750g sodium bicarbonate.

Sample No.	Amount of CO_2(g)	Maximum pH of dialysis solution	Alarm Yes/No
22	0.5	7.5	No
23	1.0	7.3	No
24	0.5	7.5	No
25	1.0	7.3	No
26	1.0	7.3	No

Table 4

This shows the results using cartridges according to the invention, containing 1g tartaric acid and 750g sodium bicarbonate.

Sample No.	Maxiumum pH of dialysis solution	Alarm Yes/No
27	7.5	No
28	7.5	No

Other tests were carried out using different "acid" solutions, and water of different pH. In each case, a cartridge according to the invention did not cause any alarm due to either high or low pH.

CLAIMS

1. A cartridge having an openable, sealed inlet and an openable, sealed outlet, for connection in-line in a haemodialysis machine for passage of water, or a solution through the cartridge, the cartridge containing sodium bicarbonate in solid form,

characterised in that the cartridge additionally contains an acid, or acid anhydride in solid form, or carbon dioxide gas.

2. A cartridge according to Claim 1, wherein the acid is in powder form.

3. A cartridge according to Claim 1 or 2, wherein the acid is citric acid.

4. A cartridge according to Claim 1 or 2, wherein the acid is tartaric acid, or another organic acid.

5. A cartridge according to any preceding claim containing at least 0.2g of acid, acid anhydride, or carbon dioxide per 1000g of sodium bicarbonate.

6. A cartridge according to Claim 5, wherein the cartridge contains at least 0.5g of acid, acid anhydride, or carbon dioxide per 1000g of sodium bicarbonate.

7. A method of preventing a temporary increase of pH in a dialysis solution being continuously produced in a haemodialysis machine from different component sources including a cartridge containing solid sodium

bicarbonate, the method comprising including in the cartridge an acid or acid anhydride in solid form, or carbon dioxide gas.

8. A method according to Claim 7, wherein the cartridge and its contents are in accordance with any one of Claims 1 to 6.

9. A method of introducing carbon dioxide gas to a cartridge according to Claim 1, wherein the carbon dioxide is introduced as dry ice.

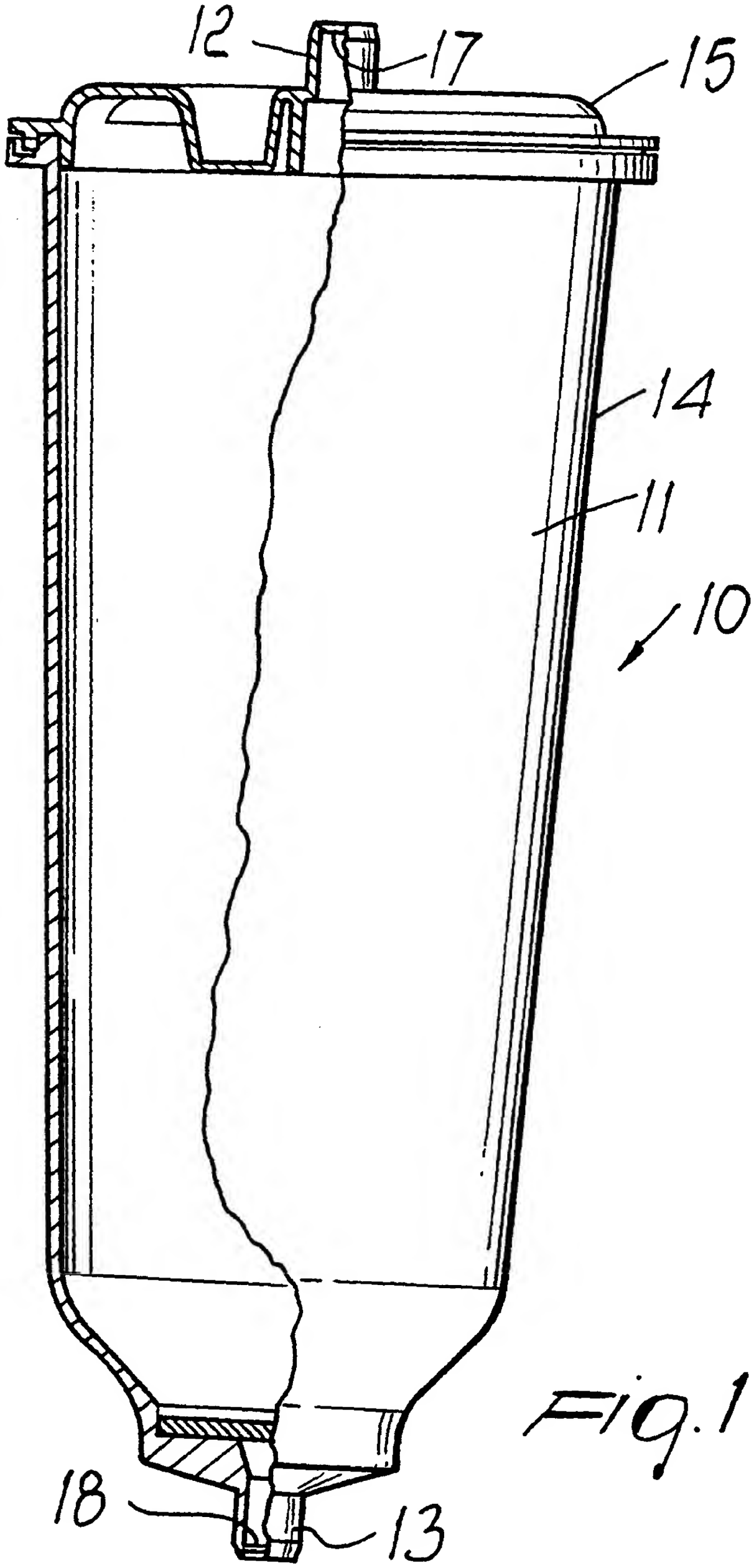

Fig.1

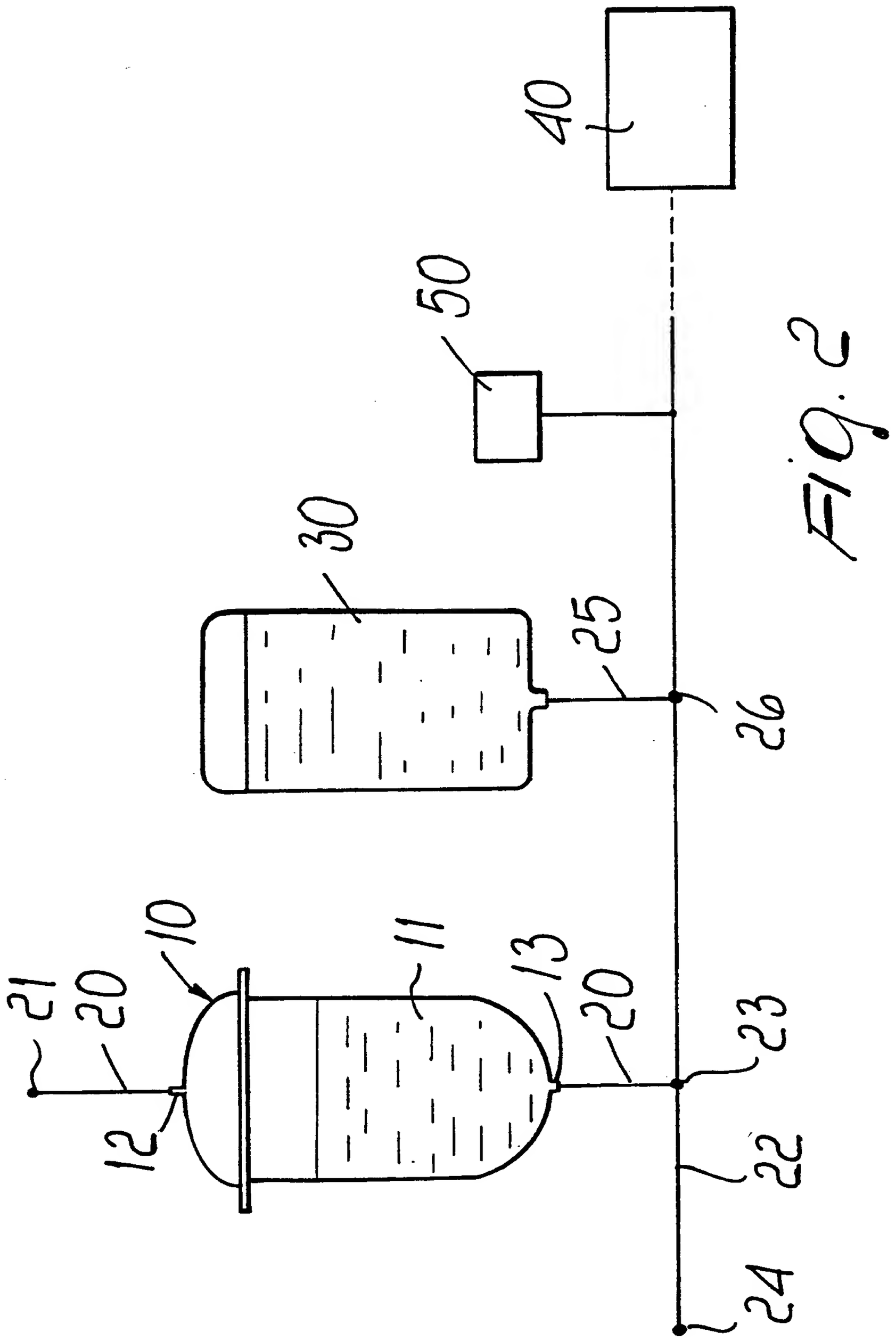

FIG. 2

INTERNATIONAL SEARCH REPORT

Inter. Application No
PCT/EP 00/00130

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M1/16 A61K33/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 11046 A (UNIV WASHINGTON) 9 July 1992 (1992-07-09) page 2, line 36 -page 4, line 9; figure 2 ---	1-8
X	EP 0 177 614 A (TOMITA PHARMA) 16 April 1986 (1986-04-16) page 4, paragraph 1 -page 5, paragraph 1 ---	1-8
X	EP 0 417 478 A (NIKKISO CO LTD ;TOWA PHARMACEUTICAL CO LTD (JP)) 20 March 1991 (1991-03-20) page 2, line 1 -page 3, line 22 ---	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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11 April 2000	26/04/2000

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Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199118 Derwent Publications Ltd., London, GB; Class B05, AN 1991-128481 XP002135441 & JP 03 066621 A (NIKKISO CO LTD), 22 March 1991 (1991-03-22) abstract	1-8
X	WO 94 25084 A (BAXTER INT) 10 November 1994 (1994-11-10) page 6, line 4 - line 25	1-8
A	WO 97 02056 A (ALTHIN MEDICAL AB ;CARLSSON PER OLOV (SE); GILLERFALK BJOERN (SE);) 23 January 1997 (1997-01-23) page 1, line 5 - line 18 page 4, line 14 - line 29; figure 1	1,7,9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter[illegible]plication No
PCT/EP 00/00130

Patent document cited in search report	Publication dat	Patent family member(s)	Publication date
WO 9211046 A	09-07-1992	CA 2098839 A	19-06-1992
		AU 7171091 A	22-07-1992
		DE 69027052 D	20-06-1996
		DE 69027052 T	26-09-1996
		DK 567452 T	14-10-1996
		EP 0567452 A	03-11-1993
		GR 3020698 T	31-10-1996
		HK 1007969 A	30-04-1999
		JP 6503233 T	14-04-1994
EP 0177614 A	16-04-1986	WO 8503435 A	15-08-1985
		US 4655941 A	07-04-1987
EP 0417478 A	20-03-1991	JP 3275626 A	06-12-1991
		JP 2986810 B	06-12-1999
		JP 3074331 A	28-03-1991
		DE 69018172 D	04-05-1995
		DE 69018172 T	09-11-1995
		US 5071558 A	10-12-1991
JP 3066621 A	22-03-1991	JP 2739898 B	15-04-1998
WO 9425084 A	10-11-1994	US 5383324 A	24-01-1995
		AT 161426 T	15-01-1998
		AU 683878 B	27-11-1997
		AU 6447394 A	21-11-1994
		CA 2138665 A	10-11-1994
		DE 69407527 D	05-02-1998
		DE 69407527 T	16-07-1998
		EP 0647145 A	12-04-1995
		ES 2113645 T	01-05-1998
		GR 3025966 T	30-04-1998
		JP 7508678 T	28-09-1995
		NZ 263691 A	26-11-1996
		SG 48702 A	18-05-1998
WO 9702056 A	23-01-1997	SE 504633 C	24-03-1997
		AU 6325996 A	05-02-1997
		CA 2223473 A	23-01-1997
		EP 0841959 A	20-05-1998
		JP 11508469 T	27-07-1999
		SE 9502397 A	04-01-1997
		US 6036858 A	14-03-2000